Introduction: brain and placenta, birth and behavior, health and disease

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This book focuses on the production and regulation of steroids, peptides, and other regulatory factors by the placenta and by maternal and fetal organs, especially brain. These regulatory factors play vital roles in the maintenance of pregnancy, the timing and onset of labor, fetal growth and development, especially the programming of fetal physiology, and maternal and fetal neural function and regulation. The maternal–placental–fetal axis is an important target for research into the regulation and control of human pregnancy. A subtext of the book is the role of maternal–placental–fetal interactions in the onset of disease and disability, especially from preterm birth and fetal programming of physiologic systems that lead to adult onset diseases, such as diabetes and hypertension. The book addresses the relationships among glucocorticoids, neuropeptides (primarily corticotropin-releasing hormone, CRH), maternal nutrition, psychosocial ‘stress’, fetal growth and development, the onset of labor, and subsequent effects on health and behavior of infants, children and adults (Figure I.1).

The placenta is not just a conduit of oxygen and nutrients from the mother to the fetus. It is not a passive organ, but rather it is very metabolically active. It metabolizes 40–60% of glucose and oxygen extracted from uterine circulation (Gluckman and Pinal, 2002, 2003). The placenta produces a large number of ‘information’ molecules, such as biologically active steroids and peptides that serve to regulate and balance maternal and fetal physiology (Petraglia et al., 1990). Once stimulated, placental hormones act on the placenta itself, and enter the maternal and fetal circulation. They act as endocrine, paracrine, and autocrine factors, to control the secretion of other regulatory factors that play functional roles in the growth, development, and maturation of the fetus, and likely have significant regulatory functions in maternal physiology and in the timing and onset of labor. Alterations in placental peptide and
steroid production and regulation will have significant effects on fetal growth and development, and can lead to intrauterine growth restriction (IUGR), and/or deviations from the normal progression toward parturition leading to preterm birth.

Many of the hormones produced by the placenta are also produced by and are active in the brain. For example, CRH, cortisol, oxytocin, vitamin D, and catecholamines are found in cells within the placenta (Petraglia et al., 1990), and in the brain. This has led some experts to suggest that the placenta performs regulatory functions that are similar, or at least analogous, to ones normally ascribed to the central nervous system. In other words, that the placenta becomes a central regulator of maternal and fetal physiology.

The first chapter of this book by Felice Petraglia and colleagues, introduces the reader to the broad array of brain, pituitary, gonadal, and adrenocortical hormones
produced by the placenta and other gestational intrauterine tissues (fetal membranes and deciduae). These peptides, steroids and monoamines are, for the most part, chemically identical and as biologically active as their hypothalamic/gonadal counterparts. Petraglia and colleagues suggest that the human placenta may be considered as a (transient) neuroendocrine organ, and a central regulator of maternal–placental–fetal physiology (Figure I.2).

Consider growth hormone (GH) production during human pregnancy. In humans, from 24 weeks gestation to parturition, maternal pituitary GH declines (and becomes effectively nonexistent). Biologically active GH-V, produced by the placenta, is secreted into maternal circulation, and appears to serve as a replacement for pituitary GH. GH-V is not regulated by GH-releasing factors, but is suppressed by elevated maternal glucose. The function of GH-V is not completely understood, but it likely serves to induce relative maternal insulin resistance, and encourages reliance on lipolysis for maternal energy metabolism (Lacroix et al., 2002).

Thus, in this instance the placenta performed a role in the regulation of maternal physiology that before pregnancy was coordinated by the central nervous system. For the developing fetus, many hormones that will eventually be produced by fetal organs are, by necessity, first provided by the placenta. The placenta is also the most likely source of factors that stimulate the cascading steps in the labor and birth process. The placenta is a central regulator of maternal and fetal physiology, ensuring appropriate physiologic milieus for normal growth and development of fetal, placental and maternal tissues necessary for successful reproduction. As such,
it offers the potential to gain insights into the role, function and mechanisms by which many hormones regulate the body.

**Preterm birth**

Despite considerable efforts, the rate of premature labor and birth has not declined (Goldenberg *et al.*, 2003; Figure I.3). This largely reflects our incomplete understanding of the processes and mechanisms underlying the timing of labor and birth. There are, as yet, no accurate diagnostic criteria to predict preterm labor or preterm birth. Nor are there therapies that have been definitively shown to delay birth once preterm labor has begun, although recent research regarding progesterone shows promise (da Fonseca *et al.*, 2003; Meis *et al.*, 2003). Clinical advances have been made in increasing the life expectancy of premature infants; but these infants still face a life of increased risk of early death, disability and disease (Regev *et al.*, 2003).

In their chapter (Chapter 2), Roger Smith and colleagues briefly review the astonishing variety of processes observed in mammalian pregnancy. There does not appear to be a single path to parturition among mammals, nor does there appear to be a single pathway leading to labour in humans, suggesting a fail-safe system. Smith and colleagues stress that a good understanding of the normal physiology which determines the timing of human birth is necessary to understand the
disturbances that occur in pathology leading to preterm birth. They review recent evidence for a number of factors involved in human parturition, including CRH, but especially the role of progesterone receptors in the final pathways of human myometrial activation.

Michael Power and Suzette Tardif review the effects of maternal nutrition on pregnancy outcome, and consider some of the possible metabolic signals involved. Epidemiologic studies and animal experiments support a role for poor maternal nutrition in preterm birth and IUGR. In developing nations, protein-energy malnutrition is, unfortunately, still a significant factor in adverse pregnancy outcome. In developed nations, excess food intake (and insufficient energy expenditure) leading to obesity and type 2 diabetes is a more significant factor, although micronutrient undernutrition (e.g. folate, calcium, vitamin C) can adversely affect pregnancy outcome. The roles of CRH, leptin and the insulin-like growth factor system in pregnancy outcome are considered.

An important subtext in this chapter and also in the chapter by Smith and colleagues is the possible role of CRH produced by the placenta in normal and pathologic pregnancy. Soon after the isolation and characterization of hypothalamic CRH by Vale and colleagues (1981), CRH was detected in maternal serum during pregnancy (Sasaki et al., 1984). The CRH gene was subsequently shown to be expressed in the human placenta (Grino et al., 1987), and to be the source of the maternal (and fetal) serum CRH. Several groups documented the pattern of increasing serum CRH concentration in normal human pregnancy (Goland et al., 1986; Campbell et al., 1987; Laatikainen et al., 1987; Sasaki et al., 1987), and the marked elevation of CRH in pregnancies complicated by multiple gestation (Warren et al., 1990) and pre-eclampsia (Laatikainen et al., 1991). Women destined to give birth prematurely exhibited both elevated CRH (Warren et al., 1992) and a precocious rise in CRH (McLean et al., 1995; Hobel et al., 1999; Leung et al., 2001; Figure I.4).

The evidence strongly supported an important role of CRH in the progression of human pregnancy to parturition. Subsequent research has supported that hypothesis, but the possibility that CRH could serve as a simple, reliable clinical marker for pregnancies at risk for delivering preterm has not panned out (McLean et al., 1999; Inder et al., 2001; Ellis et al., 2002). This may be partly explained by evidence showing that CRH has autocrine, paracrine, and endocrine actions, and may contribute to pregnancy via multiple pathways. For example, CRH may perform an autocrine, or paracrine function in the human chorion that assists in regulating prostaglandin concentrations via production of 15-hydroxy prostaglandin dehydrogenase, and thus may contribute to myometrial quiescence (not stimulation) during most of the pregnancies (McKeown and Challis, 2003).

From the comparative and evolutionary perspective, CRH remains a prime candidate for research into the regulation of human pregnancy and fetal development.
Anthropoid primates are the only species known to produce placental CRH during pregnancy (Robinson et al., 1989; Bowman et al., 2001). Understanding this apparently unique anthropoid primate adaptation may be key to understanding the normal course of human pregnancy, and metabolic disruptions of pregnancy. This will likely require the further development of nonhuman primate models of human pregnancy, fetal development, and placental function.

Origin of adult-onset disease

That events in utero affect pregnancy outcome is a fact. Preterm birth and IUGR are the most obvious, and possibly the most significant, examples of events in utero leading to postnatal morbidity and mortality. What is new is the evidence that birth outcomes heretofore considered successful might lead to poor health outcomes in adult life. Epidemiologic studies have indicated that the effects of birth size on latter disease extend into the normal birth weight range, and thus are not restricted to the serious effects of IUGR or premature birth (Barker, 1991; Barker et al., 1993; Curhan et al., 1996a, b).

This realization has led to a concerted search for mechanisms. Much of this search has centered on excessive or inappropriate activation of the HPA axis, both maternal and fetal. Activation of the fetal hypothalamic–pituitary–adrenal (HPA) axis is a common characteristic across species that results in increased output of fetal glucocorticoids, which contribute to mechanisms associated with the onset
of parturition and to the normal maturation of fetal organ systems. The fetus responds to an adverse intrauterine environment with precocious HPA activation, and premature upregulation of critical genes at each level along the axis. Thus in compromised pregnancies the fetus may be exposed inappropriately to sustained elevations of glucocorticoids.

An important theme in the chapters by Debra Sloboda and colleagues (Chapter 4) and Jonathon Seckl and colleagues (Chapter 5) is that glucocorticoids are potent steroids that have organizing effects on fetal organs. Key targets for in utero programming of physiology include glucocorticoid receptor gene expression and the CRH system. Sloboda and colleagues review data from animal models concerning the effects of exogenous glucocorticoids on pregnancy and fetal development.

The use of glucocorticoids to mature fetal lung tissue prior to preterm birth has had a significant positive effect on neonatal morbidity and mortality. A single course of antenatal corticosteroids significantly reduces the risk of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal mortality, although it does not reduce the overall incidence of chronic lung disease (Dudley et al., 2003; Figure I.5). However, animal studies, such as the one described in Chapters 4 and 5, have demonstrated that glucocorticoid administration in late gestation can result in IUGR and significant alterations in metabolic and HPA axis function and regulation. This raises cautionary warnings concerning both the use of multiple doses of glucocorticoids to mature fetal lung tissue in pregnancies at risk for preterm birth, and the accuracy with which pregnancies at risk for preterm

Figure I.5 A single course of antenatal steroids significantly decreases the risk of neonatal death, RDS, and IVH, but does not decrease the incidence of chronic lung disease. Data (means and 95% confidence intervals) are from Dudley et al. (2003)
birth can be predicted. The administration of glucocorticoids to a fetus that is carried to term may not be benign.

Seckl and colleagues review the evidence (epidemiologic and physiologic) concerning the programming of fetal physiology in utero. They present the case that glucocorticoids play important roles in both appropriate and inappropriate programming. They discuss the placental enzyme 11β-hydroxysteroid dehydrogenase type 2, which acts as a barrier to glucocorticoids. Regulation of this enzyme may serve to increase or decrease fetal exposure to maternal glucocorticoids. They discuss programming of the cardiovascular system, liver, pancreas, and brain by glucocorticoids and the subsequent increased vulnerability to adult onset diseases such programming can engender.

Elysia Davis and colleagues continue the theme of stress, HPA activation, glucocorticoids and their effects on pregnancy. Their focus is on human behavior and human data. They discuss a neurobiologic model in which maternal psychosocial stress influences developmental outcomes that are mediated, in part, via maternal–placental–fetal neuroendocrine mechanisms. They present data on the consequences of stress during pregnancy on neuroendocrine processes and fetal and infant development. They also note the uniqueness of placental CRH in anthropoid primates, and that placental CRH and cortisol may contribute to the organization of the fetal central nervous system (Sandman et al., 1997; Florio and Petraglia, 2001).

**Feed-forward regulation of CRH by glucocorticoids**

Until recently, it was the received view that glucocorticoids restrained CRH production. The model system was the HPA axis, wherein hypothalamic CRH stimulated pituitary adrenocorticotropic hormone (ACTH) production, which in turn stimulated cortisol production by the adrenals. Cortisol crossed the blood–brain barrier and exerted negative feedback on CRH neurons in the hypothalamic paraventricular nucleus (PVN), restraining the system. It is a curious fact that independent groups of researchers, working on different CRH producing organs (the brain and the placenta) found at roughly the same time that glucocorticoids can also stimulate CRH production. Glucocorticoid added to cultured human placental tissue resulted in the upregulation of CRH gene expression (Robinson et al., 1988; Jones et al., 1989; Figure I.6). In several regions of the brain (e.g. amygdala and bed nucleus of the stria terminalis, and areas of the paraventricular region of the hypothalamus that project to the brainstem) CRH messenger ribonucleic acid (mRNA) expression similarly is upregulated by glucocorticoids (Swanson and Simmons, 1989; Makino et al., 1994; Watts and Sanchez-Watts, 1995; Figure I.7).
The majority of CRH neurons within the PVN are clustered in the parvicellular division. Other regions with predominant CRH-containing neurons are the lateral bed nucleus of the stria terminalis and the central region of the central nucleus of the amygdala (CeA). To a smaller degree, there are CRH cells in the lateral...
hypothalamus, prefrontal and cingulate cortex. In brainstem regions, CRH cells are clustered near the locus coeruleus (Barringtons' nucleus) (Valentino et al., 1995), parabrachial region and regions of the solitary nucleus (Figure I.8).

In this volume, Watts reviews neural regulation of CRH axons. He emphasizes that there is cell specificity in how CRH and the CRH gene is regulated. Glucocorticoids repress CRH gene expression in the hypothalamic paraventricular nucleus (the familiar negative feedback system of the HPA axis), but in other regions (e.g. CeA) glucocorticoids stimulate CRH gene expression, and in others glucocorticoids have no effect at all. Even within the PVN, basal levels of glucocorticoids appear necessary to sustain CRH gene expression. Adrenalectomized rats show a suppressed CRH response in the PVN to hypovolemia rather than an exaggerated response (Tanimura and Watts, 2000). It turns out that the 'usual' negative restraint of CRH by glucocorticoids has actually only been seen in one (admittedly important) set of CRH expressing neurons. Thus the increase in human placental CRH mRNA expression when exposed to glucocorticoids does not appear to represent an unusual circumstance. The current state of knowledge supports the idea that glucocorticoids have variable effects on CRH regulation depending on cell type, and intracellular and extracellular factors. The original idea of glucocorticoids functioning as a negative feedback response molecule has been expanded to a more flexible, context-oriented understanding of regulation.

Figure I.7  Corticosterone decreases CRH expression in the rat PVN but increases CRH expression in rat central nucleus of the amygdala (CeA). From Makino et al. (1994), with permission.